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COMPLETE SPECIFICATION

(54) DERIVATIVES OF 4-AMINOBUTYRIC ACID AND DRUGS, ACTIVE IN PARTICULAR ON THE CENTRAL NERVOUS SYSTEM, CONTAINING SAME.

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Price 90p

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Exhibit 3

The present invention relates to derivatives of 4-amino butyric acid having pharmacological properties on the central nervous system.

More particularly, the invention relates to amides of 4-amino butyric acid corresponding to the general formula:

$$R\text{-}CONH\text{-}(CH_2)_m\text{-}\underset{X}{CH}\text{-}(CH_2)_n\text{-}CON\begin{cases}R_1\\R_2\end{cases} \qquad (I)$$

in which:

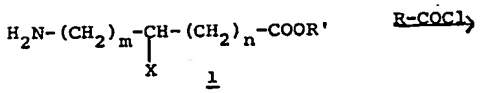
- R designates a linear or branched alkyl group having from 1 to 7 atoms of carbon or a cycloalkyl group;
- m represents an integer of from 0 to 3;
- n represents an integer of from 0 to 2, on condition that m+n is equal to or greater than 1;
- X represents hydrogen, a lower alkyl group (1 to 4 carbon atoms), a phenylalkyl group in which the phenyl group is optionally substituted;
- R_1 and R_2 considered separately designate hydrogen, a linear or branched alkyl group having from 1 to 18 carbon atoms, an aralkyl group, a cycloalkyl group or an optionally substituted phenyl group; or

R_1 and R_2 considered together with the atom of nitrogen to which they are attached represent a heterocycle with 5 or 6 groupings possibly comprising a second heteroatom, such as pyrrolidine, morpholine, piperazine or pyridine and its partially or totally hydrogenated derivatives.

The compounds of the invention show interesting activities on the central nervous system and may be used in particular as sedatives, tranquilizers, hypnotics and minor tranquilizers.

In DE-A-1 927 692 chemical products are described the formula of which differs from that of the products (I) with regard to the nature of the radical R; the products of said German Patent are indicated as having an anticonvulsant, sedative or hypnotic type of neurological activity, but it does not seem that said products react to actographic tests, to potentialisation of narcosis and antagonism of convulsions provoked by bicuculline or electroshock as do the products of formula (1).

The compounds according to the invention may be obtained according to the following reaction diagram:



(R' being H or a lower alkyl radical)

$$RCONH-(CH_2)_m-\underset{\underset{X}{|}}{CH}-(CH_2)_n-COOR' \xrightarrow{HN\begin{smallmatrix}R_1\\R_2\end{smallmatrix}} RCONH-(CH_2)_m-\underset{\underset{X}{|}}{CH}-(CH_2)_n-CON\begin{smallmatrix}R_1\\R_2\end{smallmatrix}$$

(2)

From the known composite aminoacids or aminoesters 1, the amide acids 2 are obtained by action of the chloride of R-COCl acid within a suitable solvent, such as water, ether or a lower aliphatic alcohol and in the presence of an acceptor of inorganic or organic hydracid and, in particular, sodium hydroxide or triethylamine.

The amide acids or esters 2 are isolated from the reaction mixture and, most often, are used as such without purification for the following step.

Amidification (reaction with $HN\begin{smallmatrix}R_1\\R_2\end{smallmatrix}$) may be effected according to various methods.

When R' represents a lower alkyl radical, the reaction is made of the ester 2 on the amine $HN\begin{smallmatrix}R_1\\R_2\end{smallmatrix}$ in solution in a lower aliphatic alcohol or using an excess of amine as solvent. Operation is generally carried out at a temperature of between about 0 and about 50°C and, most often, at ambient temperature. The duration of the reaction may vary from an hour to several days. When R' represents hydrogen, the reaction of the acid 2 on the amine $HN\begin{smallmatrix}R_1\\R_2\end{smallmatrix}$ is made either by passing through the intermediary of the corresponding ester (conversion of acid into an ester of lower aliphatic alcohol) or by using a mixed anhydride formed from the acid 2. This mixed anhydride is formed by reacting the acid on ethylchloroformate in the presence of an alkaline agent such as triethylamine. Operation is carried out in a suitable solvent such as tetrahydrofuran without it being necessary to isolate the mixed anhydride obtained. Operation is generally carried out at a temperature of between 0 and 40°C for a duration which may vary from 3 to 15 hours, about.

The following non-limiting examples will enable the scope of the invention to be more readily understood.

Example 1

10-Butyl-4,9-dioxo-5,10-diaza-tetradecane (CM 40039)

(I) R = CH_3-$(CH_2)_2$-; m = n = 1; X = H; R_1 = R_2 = -$(CH_2)_3CH_3$

a) To a solution of 10.3 g of 4-amino butyric acid in 110 ml of a 2N aqueous solution of sodium hydroxide cooled in ice, are added, drop by drop, with stirring, 11.7 g of butyryl chloride. After the end of the addition, stirring is continued for 4 hours.

The aqueous solution is washed with methylene chloride, then the aqueous phase is acidified and saturated with sodium chloride. It is extracted with methylene chloride, dried over sodium sulfate and evaporated to dryness in vacuo. The solid residue is stirred three times with pentane (300 ml) then dried in vacuo. Weight 9.1 g used as such for the following operation.

b) the acid obtained hereinabove (9.1 g) is dissolved in 200 ml of dry tetrahydrofuran. 6.06 g of triethylamine and 6.51g of ethyl chloroformate are added, maintaining the temperature lower than or equal to 5°C. It is left 1 hour with stirring, then 7.74 g of dibutylamine are added drop by drop. It is left one night with stirring at ambient temperature.

The insoluble substance is filtered and the solvent is evaporated to dryness. The residue is taken up in ether and the solution is washed with a dilute solution of hydrochloric acid, then with a dilute solution of sodium hydroxide and , finally, with a saturated aqueous solution of sodium chloride. The ethereal solution is dried over sodium sulfate, the solvent is evaporated to dryness and the residue is distilled in vacuo. 6.2 g of a pale yellow liquid are obtained, bp/0.01 mm: 170°C.

Example 2

Operation is carried out as in Example 1, but varying the amine used in paragraph b).

The products (I): R = $CH_3(CH_2)_2$, m = n = 1, X = H shown in Table I hereinafter are thus obtained.

Example 3

Operation is carried out as in Example 1, but varying, on the one hand, the acid chloride used in the first step and, possibly, on the other hand, the amine used in the second step.

The products (I) shown in Table II hereinafter are thus ob-

tained.

Example 4

5-Butyl-12-ethyl-13-methyl-6,11-dioxo-5,10-diaza-pentadecane (CM 40195)

(I) R = CH_3CH_2-$\underset{CH_3}{\underset{|}{CH}}$—$\underset{C_2H_5}{\underset{|}{CH}}$- ; m = n = 1; X = H; R_1 = R_2 = -$(CH_2)_3CH_3$

a) To 9.18 g of the hydrochloride of the benzyl ester of 4-amino butyric acid dissolved in 100 ml of tetrahydrofuran, are added 8.08 g of triethylamine. The mixture is cooled by an ice bath, then 6.5 g of chloride of 2-ethyl-3-methyl- pentanoic acid are added drop by drop. It is left one night with stirring at ambient temperature, then the reaction mixture is filtered and the solvent is evaporated to dryness.

The residue is taken up in ethyl acetate, washed with water then with a dilute solution of sodium hydroxide, again with water, then with a dilute solution of hydrochloric acid and, finally, with a saturated solution of sodium chloride. The solution is dried over sodium sulfate and the solvent is evaporated to dryness in vacuo.

11 g of the benzyl ester of the 7-ethyl-8-methyl-6-oxo-5-aza-1-decanoic acid are thus obtained. This ester (11g) is dissolved in 150 ml of 96 ethanol and hydrogen at atmospheric pressure in the presence of 1 g of palladium on charcoal with 10% of palladium. At the end of the reaction, the catalyst is filtered and evaporated to dryness in vacuo. To the residue taken up in the anhydrous ether (100 ml) are added 6 g of dicyclohexylamine and the mixture is left one night at 0°C. The salt formed is dewatered and washed with ether. Weight: 7.8 g.

The salt thus obtained is dissolved in 100 ml of water. The solution is cooled in ice and acidified by concentrated hydrochloric acid up to pH = 1.5. The solution of sodium chloride is saturated and extracted with ethyl acetate. The organic solution is washed three times with a saturated solution of sodium chloride , dried over sodium sulfate and evaporated to dryness.

3.9 g of 7-ethyl-8-methyl-6-oxo-5-aza-1-decanoic acid are thus obtained.

b) According to the technique of Example 1 b), dibutylamine is reacted on this acid. In the same way, CM 40195 is obtained in the form of an oil; b.p./0.01mm: 200°C.

Example 5

4,12-Dioxo-5,13-diaza- heptadecane (CM 40387)

(I) R = $CH_3CH_2CH_2$-; m = 3; n = 2; X = H; R_1=H; R_2=$(CH_2)_3CH_3$

a) To a solution, cooled in ice, of 5.2 g of 7-amino heptanoic acid in 80 ml of 4N sodium hydroxide, are slowly added with stirring, 4.8 g of butyryl chloride. Stirring is continued for 4 hours, then the mixture is acidified up to pH = 2 by hydrochloric acid. It is extracted with ethyl acetate, the solution is dried over sodium sulfate and the solvent is evaporated to dryness in vacuo.

An oil (4.2g) is obtained which crystallises. It is recrystallised in hexane; melting point by the Koffler method (m.p.k) 68°C.

b) To the solution of 2.3 g of the acid obtained previously in 30 ml of dry tetrahydrofuran, are added 1.1 g of triethylamine, then 1.2g of ethyl chloroformate. It is left 2 hours with stirring, then the solution of 0.85 g of butylamine in 5 ml of tetrahydrofuran is slowly added. It is left with stirring for 15 hours at ambient temperature, then water is added and extracted with ethyl acetate. The organic solution is washed with a solution of sodium carbonate, dried over sodium sulfate and the solvent is evaporated to dryness. The residue is recrystallised in acetonitril ; m.p.k: 132°C.

Example 6

By operating as in Example 5 from different aminoacids 1 and by varying the reagents R-COCl and $\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!\!NH$, the products (I) shown in Table III hereinafter are obtained.

Example 7

2,7-Dioxo-1,6-diaza- decane (CM 40401)

(I) R = $CH_3(CH_2)_2$-; m = n = 1; X = H; R_1 = R_2 = H.

a) To a solution of 17 g of 6-oxo-5-aza - 1-nonanoic acid (obtained according to example 1 a)) in 500 ml of absolute ethanol, are added 10 ml of concentrated sulfuric acid and the mixture is stirred for 4 days at ambient temperature. The solvent is evaporated at 30°C in vacuo and the residue is taken up in icy water. The mixture is neutralised by addition of sodium bicarbonate, then extrac-

ted with methylene chloride. It is dried over sodium sulfate and evaporated to dryness.

16 g of the expected ethyl ester are obtained.

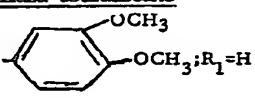
b) the 16 g of ethyl ester obtained hereinabove are introduced in 300 ml of a 16% solution of ammonia in methanol. Stirring is carried out for 5 days at ambient temperature. The solvent is evaporated to dryness and the residue is taken up by ether. The solid is dewatered and washed with acetonitrile.

Colourless crystals (10 g) are obtained. m.p.k: 135°C (acetonitril).

Example 8

6-(3,4-dimethoxy-benzyl)-4,9-dioxo-5,10-diaza-tetradecane

(CM 40187)

(I) R = $CH_3CH_2CH_2$- m=0; n=2; X= -CH_2-  ; R_1=H

R_2 = -$(CH_2)_3CH_3$

Operation is carried out as in Example 7, replacing in the first reaction the 4-chloro benzoyl chloride by an equivalent quantity of butyryl chloride.

In the same way, the expected compound is obtained in the form of a colourless solid; m.p.k: 152°C.

The products according to the invention have been subjected to various tests concerning their pharmacological activity and, in particular, their action on the central nervous system.

A) Pharmacological activity

1) Sedative and hypnotic effect

a) Study of the actograph

The measurement of the actograph is carried out in the mouse 45 mins. after the product has been administered. Operation is carried out on batches of 12 animals, each being isolated for 10 mins. before measurement. The counting of the scores is effected by cutting of two perpendicular light beams.

Table IV hereinafter shows the results obtained with various products of the invention administered at the dose of 500 mg/kg per os. The results are expressed in percentage of variation of the scores obtained with respect to control animals which have not been treated.

The products are noted to be distributed in two groups:
- those provoking hypomotility such as 40217, 40039, 40271, 40272, 40319; in the event of the treated animals showing a loss of the turning-round reflex, which translates the actual effect of narcosis of the product, PRR has been noted;
- those provoking hypermotility, such as 40142, 40398, 40397, 40404, 40253, 40355, 40209; to specify the results obtained, the study for two products has been repeated in dose-effect according to the same protocol.

The results obtained are shown in Table V hereinafter.

b) Potentialisation of narcosis by pentobarbital

The products to be studied were administered per os in the mouse at a dose of 500 mg/kg, 1 hour before the pentobarbital injected by the intraperitoneal route at a rate of 20 mg/kg.

The percentage of the animals having lost the turning-around reflex is determined. The results are expressed in percentage or, in some cases, in effective dose 50 (ED 50) or dose provoking narcosis in 50% of the animals treated.

The results are shown in Table VI hereinafter.

c) Electroencephalographic study

In order better to understand the hypnotic activity of the products according to the invention, an electroencephalographic study has been effected on one of them, namely CM 40039.

The 40039 is studied at the dose of 350 mg/kg p.o. in three rats. After a period of habituation of 10 days (lightened period from 8 a.m. to 8 p.m. and dark period from 8 p.m. to 8 a.m.) the animals are recorded for 5 days with the solvent (10% gum arabic), then recorded for 4 days during which they receive the product at 9 o'clock each morning. After this chronic administration, the animals are recorded the following 5 days (checking period).

Results:

The animals are recorded 24 hours out of 24. The statistical study is made on sections of 24 hours. An overall analysis is made on the three rats by accumulating the 15 control days, the 12 days of treatment, the 15 checking days. In each hourly section of 24 hours, the arouse time (EV), slow sleep (SL), paradoxal sleep (SP), total sleep (ST), as well as the ratio (in %) paradoxal sleep/total

sleep (SP/ST) are evaluated (cf. Table VII hereinafter).

During the whole period of study, the recordings have not shown any morphological changes of the encephalographic outline.

The product provokes a significant reduction in waking (-8,1%) correlated to a significant increase in the slow sleep (+6.6%).

This effect persists during the checking phase.

2) antiepileptic effect

The antiepileptic effect was determined vis-à-vis convulsive crises provoked by electroshock or by bicuculline.

Electroshock (12.5 V for 0.5 sec) is effected in the mouse 60 mins. after administration of the product by the oral route.

Bicuculline is administered to the mouse by the intravenous route at a rate of 1 mg/kg, 60 mins. after the product to be studied has been given per os. The protector effect obtained vis-à-vis the tonic crises is noted.

By operating on various batches of animals with different doses of the product to be studied, the median effective dose (ED 50) can be determined.

The results are shown in Table VIII hereinafter and show the clear antiepileptic properties of the products studied.

B) Biochemical study

a) Effect on the rate of 4-aminobutyric acid

The 40039 was administered 30 mins. before sacrifice in the mouse. The rate of 4-aminobutyric acid was evaluated on the whole brain (batch of 6 animals) (cf. Table IX hereinafter).

The 40039 provokes a rapid increase in the rate of 4-aminobutyric acid in the whole brain in the mouse.

b) Effect on the central dopaminergy

The effect of the products on the central dopaminergic activity was studied by measurement of the accumulation of homovanillic acid over a period of 24 hours after adminstration of the products in the mouse.

The rate of homovanillic acid (HVA) is evaluated in the whole brain, the animals receive an injection of probenecidum

(200 mg/kg i. p.) an hour and a half before sacrifice (batch of 10 animals).

The two products provoke similar effects on the rate of HVA, in particular, they provoke an increase in the rate 4 hours after their administration and a considerable reduction 24 hours after their administration (cf. Table X hereinafter).

c) Acute toxicity

The products to be studied are administered by the oral route at doses of 500 and 1000 mg/kg to batches of mice. The mice are observed for 24 hours and the mortality is noted.

The results expressed in percentage of mortality are shown in Table XI hereinafter.

They indicate that, at the dose of 500 mg/kg, none of the products studied showed any sign of acute toxicity. At 1000 mg/kg, a very high dose, a few products show a 100% toxicity, but, in the majority of cases, acute toxicity remains low or zero.

The tests thus carried out show that the products according to the invention present interesting pharmacological properties and a low toxicity. Consequently, they may be used in human therapeutics, particularly for the treatment of neurological and psychic disorders.

In particular, the products according to the invention may be used for treating disorders in mood or behaviour; nervosism, irritability as well as for treating anxious states and insomnia.

These products may be administered by the oral route or by injectable route. The pharmaceutical compositions may be solid or liquid and may be in the form, for example, of tablets, capsules, granules, suppositories or injectable preparations.

The dosage may vary to wide proportions, in particular depending on the type and seriousness of the disorder to be treated and according to the mode of administration. Most often, in the adult, by the oral route, it is included between 0.100 and 1 g per day, possibly spread out in several doses.

By way of examples of pharmaceutical compositions, the following preparations may be cited:

Capsules

CM 40039 at 100 mg	
CM 40039	100 mg
Aerosil	0.5 mg
Magnesium stearate	1.5 mg
Starch STA RX 1500	48 mg
	150 mg

Tablets

CM 40142 at 200 mg	
CM 40142	200 mg
Microcrystalline cellulose	100 mg
Lactose	197 mg
Magnesium stearate	3 mg
	500 mg

TABLE I

$CH_3-(CH_2)_2-CO-NH-(CH_2)_3-CO-N\begin{matrix}R_1\\R_2\end{matrix}$

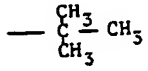
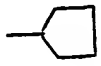
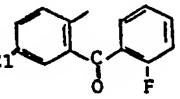
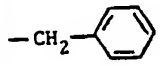
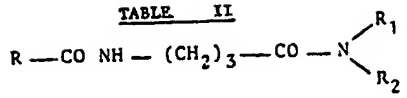
Code number	R_1	R_2	Melting point (°C) (solvent of cristallisation) or boiling point [°C (pressure)]
40 142	H	$-(CH_2)_3CH_3$	120,5 (acetonitrile)
40 205	H	$-(CH_2)_7-CH_3$	118 (acetonitrile)
40 206			84 (precipitated and washed with ether)
40 207	H		102 (")
40 208			62 (")
40 209	H		134 (")
40 210	H		122 (isopropanol)
40 211			~ 50°C (décomposition)
40 216	$-CH(CH_3)-CH_2-CH_3$	$-CH(CH_3)-CH_2-CH_3$	b.p. : 185-190 (0,01 mm)
40 217	$-(CH_2)_2-CH_3$	$-(CH_2)_2-CH_3$	b.p. : 190-194 (0,01 mm)
40 218	H	$-C_{18}H_{37}$	124 (acetonitrile)
40 219			60 (anhydrous ether)
40 252	H	$-CH_2CH_2OH$	102 (acetonitrile)
40 316	H		132 (acetonitrile)
40 396	H	$-CH_3$	100 (acetonitrile)
40 398	H	$-(CH_2)_2CH_3$	130 (acetonitrile)

TABLE I (cont.)

Code number	R_1	R_2	Melting point (°C) (solvent of cristallisation) or boiling point [°C (pressure)]
40 463	H	$-CH_2CH_3$	124 (acetonitrile)
40 466	H	$-CH(CH_3)_2$	124 (acetonitrile)
40 521	H	$-(CH_2)_4CH_3$	110 (acetonitrile)
40 532	H		124 (acetonitrile)
40 947	H	$-(CH_2)_5-CH_3$	110 (acetonitrile)
40 984	$-(CH_2)_4-CH_3$	$-(CH_2)_4-CH_3$	Oil (chromatographed)
40 987	H	$-CH(CH_3)-CH_2CH_3$	97 (acetonitrile)
40 988	H	$-CH_2CH_2-CH(CH_3)_2$	108 (acetonitrile)
40 989	H	$-C(CH_3)_2-CH_2CH_3$	72 (acetonitrile)
40 990	H	$-CH_2-C(CH_3)_3$	70 (acetonitrile)

TABLE II



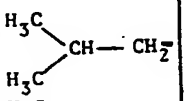
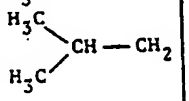
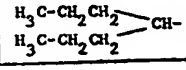
Code number	R	R_1	R_2	Melting point (°C) Boiling point [°C(pressure)]
40 254		H	$(CH_2)_3-CH_3$	88 (ether)
40 272		$-(CH_2)_3CH_3$	$-(CH_2)_3-CH_3$	b.p: 165-167 (0,01 mm)
40 273	$CH_3-(CH_2)_6-$	H	$-(CH_2)_3-CH_3$	118 (acetonitrile)
40 274	$CH_3-(CH_2)_6$	$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$	b.p: 210-215 (0,01 mm)
40 417		H	$-(CH_2)_3-CH_3$	110 (ethyl acetate)
40 418		H	$-(CH_2)_2-CH_3$	122 (acetonitrile)
40 440		H	$-(CH_2)_2-CH_3$	141 (acetonitrile)
40 443		H	$-(CH_2)_3-CH_3$	145 (acetonitrile)
40 462		$-(CH_2)_3-CH_3$	$-(CH_2)_3-CH_3$	b.p: 184 (0,01 mm)
40 467		H	$-(CH_2)_3-CH_3$	98 (acetonitrile)
40 885		H	$-(CH_2)_3CH_3$	128 (acetonitrile)

TABLE III

Code number	R	m	n	X	R_1	R_2	Melting point °C (°C) boiling point °C (pressure)
40 215	CH_3-	2	2	H	$-(CH_2)_3-CH_3$	$-(CH_2)_3CH_3$	69 (ether-hexane)
40 253	$CH_3-(CH_2)_2-$	1	0	H	H	$-(CH_2)_3CH_3$	170 (ether)
40 271	$CH_3-(CH_2)_2-$	1	0	H	$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$	b. p.: 165-7 (0,01 mm)
40 318	$H_3C-C(CH_3)_2-$	1	0	H	H	$-(CH_2)_3CH_3$	74 (precipitated)
40 319	$H_3C-C(CH_3)_2-$	1	0	H	$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$	b. p.: 136-140 (0,01 mm)
40 386	$H_3C-C(CH_3)_2-$	3	2	H	H	$-(CH_2)_3CH_3$	82 (isopylic benzene ether)
40 395	$CH_3-(CH_2)_2$	0	1	$-CH_3$	H	$-(CH_2)_3CH_3$	154 (acetonitrile)
40 397	$CH_3-(CH_2)_2$	0	2	$-CH_3$	H	$-(CH_2)_3CH_3$	110 (acetonitrile)
40 404	$CH_3-(CH_2)_2$	2	0	$-CH_3$	H	$-(CH_2)_3CH_3$	100 (acetonitrile)

TABLE IV

N° Products	Measurement of actograph (p. cent scores/controls)
40 217	- 37 *
40 039	PRR
40 206	- 8
40 271	- 53 **
40 401	- 20
40 398	+ 54 **
40 142	+ 50 **
40 316	+ 16
40 395	- 35
40 397	+ 91 **
40 404	+ 52 **
40 272	- 47 **
40 319	- 51 **
40 253	+ 33 *
40 355	+ 62 **
40 209	+ 36 *
40 254	- 2

TABLE IV (cont.)

N° Products	Measurement of actograph (p. cent scores/ controls)
40 386	- 57 **
40 417	+ 56 **
40 418	+ 93 **
40 443	+ 78 **
40 463	+ 41 **
40 466	+ 97 **
40 467	+ 115 **
40 521	+ 101 **
40 947	+ 37 *

* $p \leqslant 0,05$ ** $p \leqslant 0,01$

TABLE V

Dose effect of 40 039 and of 40 142 on actograph.

CM 40 039				
Dose (mg/kg p. os)	20	40	80	160
p. cent scores/controls	- 30 X	- 38 XX	- 37 XX	- 28
X p ⩽ 0,05 XX p ⩽ 0,01				

CM 40 142				
Dose (mg/kg p. os)	100	200	300	400
p. cent scores/controls	+ 1	+ 31	+ 38 XX	+ 50 XX
XX p ⩽ 0,01				

TABLE VI

N° Products	Percentage of animals in narcosis at 500 mg/kg p. os or dose (p. os) provoking 50 % of induction of narcosis (ED 50)
40 217	0
40 039	ED 50 = 200
40 216	100
40 206	0
40 271	100
40 401	0
40 398	ED 50 = 350
40 142	ED 50 = 297
40 316	70
40 395	70
40 397	100
40 404	40
40 272	72
40 319	ED 50 = 175
40 253	50
40 355	40
40 254	50
40 318	90
40 443	40
40 462	30
40 466	30
40 984	60
40 989	50

TABLE VII

Analysis of the encephalographic outline per hourly section of 24 hours

	Controls	Treated 40039 (325 mg/kg)	Check
EV	44,2 ± 3,3	40,6 ± 3 XXX - 8,1	40,3 ± 3,6 XXX - 8,8
SL	48,3 ± 2,5	51,5 ± 2 XXX + 6,6	51 ± 3 XX + 5,6
SP	7,6 ± 1,4	8,1 ± 1,4 n.s. + 6,6	8,6 ± 1,7 X + 13,2
ST	55,9 ± 3	59,5 ± 2,6 XXX + 6,4	59,6 ± 3,9 XXX + 6,6
SP/ST	12,8 ± 2,1	13,2 ± 1,9 n.s. + 3,1	13,5 ± 1,8 n.s. + 5,5

X $p \leqslant 0,1$ XX $p \leqslant 0,05$ XXX $p \leqslant 0,01$

TABLE VIII

N° Products	Median effective dose of protection from tonic crises (ED 50) (mg/kg p. os)	
	Bicuculline	Electroshock
40 039	300	250
40 142	325	150
40 253	< 500	500
40 254	< 500	-
40 271	< 500	500
40 379	450	-
40 418	300	-
40 462	150	500
40 463	380	-
40 467	150	< 500
40 521	250	180
40 947	250	400

TABLE . IX

	Controls	Treated 40039 500 mg/kg p. os	p.cent/controls
Rate of amino butyric acid in. µg/g brain	280 ± 8	321 ± 12 *	14,6
* $p \leqslant 0,05$			

TABLE . X

Rate of HVA in ng/g ..					
	0	2 hrs.	4 hrs.	6 hrs.	24 hrs.
40 039 500 mg/kg p.os	658 ± 40	798 ± 34 + 21 % X	894 ± 37 + 36 % XX	659 ± 29 0 %	441 ± 19 - 33 % XX
40 142 500 mg/kg p.os	521 ± 29	379 ± 11 - 27 % XX	793 ± 52 + 52 % XX	571 ± 23 + 9	290 ± 16 - 44 XX
X $p \leqslant 0,05$ XX $p \leqslant 0,01$					

TABLE XI

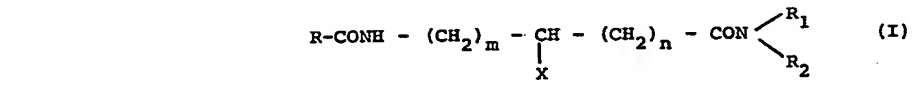
N° Product	p. cent of mortality	
	at 500 mg/kg p. os	at 1000 mg/kg p. os
40 039	0	100
40 142	0	0
40 206	0	0
40 209	0	20
40 216	0	100
40 217	0	0
40 253	0	0
40 254	0	20
40 271	0	100
40 272	0	0
40 316	0	0
40 319	0	0
40 355	0	0
40 395	0	20
40 397	0	20
40 398	0	0
40 401	0	0
40 404	0	0

TABLE XI (cont.)

N° Product	p. cent of mortality	
	at 500 mg/kg p. os	at 1000 mg/kg p. os
40 417	0	20
40 418	0	0
40 443	0	0
40 462	0	0
40 463	0	0
40 466	0	0
40 467	0	0
40 581	0	0
40 947	0	0
40 984	0	100
40 989	0	80

CLAIMS:

1. An amide of 4-aminobutyric acid corresponding to general formula:



(I)

in which:
- R designates a linear or branched alkyl group having from 1 to 7 carbon atoms or a cycloalkyl group;
- m represents an integer of from 0 to 3;
- n represents an integer of from 0 to 2, on condition that m+n is equal to or greater than 1;
- X represents hydrogen, a lower alkyl group (1 to 4 carbons), a phenylalkyl group in which the phenyl group is optionally substituted,
- R_1 and R_2 considered separately designate hydrogen, a linear or branched alkyl group having from 1 to 18 carbon atoms, an aralkyl group, a cycloalkyl group or an optionally substituted phenyl group,
- or R_1 and R_2 considered together with the nitrogen atom to which they are attached represent a heterocycle with 5 or 6 groupings optionally comprising a second heteroatom,such as pyrrolidine, morpholine, piperazine or pyridine and its partially or totally hydrogenated derivatives.

2. An amide according to Claim 1, wherein R is the CH_3-$(CH_2)_2$- group; m=n=1; X is hydrogen and R_1=R_2=-$(CH_2)_3$-CH_3.

3. An amide according to Claim 1, wherein R is the CH_3-$(CH_2)_2$- group, m=n=1; X is hydrogen, R_1 is hydrogen and R_2 is the -$(CH_2)_3$-CH_3 group.

4. A process for preparing an amide according to Claim 1, wherein the starting product is constituted by an aminoacid of formula:

$$H_2N - (CH_2)_m - \overset{X}{\underset{|}{CH}} - (CH_2)_n - COOR'$$

in which m, n and X have the meanings given in Claim 1 and R' is a hydrogen atom or a lower alkyl group (1 to 4 carbon atoms), said product is reacted with an acid chloride of formula R CO Cl so as to convert the amide of the starting product into an amide radical and the product obtained is subjected to an amidification with a product of formula $HN\begin{matrix}R_1\\R_2\end{matrix}$, wherein R_1 and R_2 are as defined in Claim 1.

5. The process according to Claim 4, wherein amidification is effected by reaction of a product in which R' is lower alkyl with the amine $HN\begin{matrix}R_1\\R_2\end{matrix}$, operating in solution in alcohol or using an excess of amine as solvent, and at a temperature of between about 0 and about 50°C.

6. The process of Claim 5, wherein amidification of an acid (R'=H) which is previously converted into ester of a lower alcohol is effected.

7. The process of Claim 4, wherein amidification is effected on a mixed anhydride of the acid (R'=H) by action on the acid of an ethyl chloroformate in the presence of an alkaline agent such as triethylamine.

8. A pharmaceutical composition particularly useful for the treatment of neurological and psychic disorders, which comprises, as active ingredient, at least one product according to Claim 1 in association with a pharmaceutically acceptable carrier or excipient therefor.

9. A pharmaceutical composition according to claim 8, which is prepared with a view to daily administration to man at a dose of 0.1 to 1g in one or several doses.

10. A pharmaceutical composition according to Claim 9, which is prepared with a view to oral administration.

11. A pharmaceutical composition according to Claim 9, which is prepared with a view to administration by injection.

12. An amide of a 4-aminobutyric acid of the general formula (I) given and defined in Claim 1, which is any one of those specifically hereinbefore mentioned.

13. A process for the preparation of an amide of a 4-aminobutyric acid of the general formula (I) given and defined in Claim 1, substantially as hereinbefore described with particular reference to the accompanying Preparatory Examples.

14. An amide of a 4-aminobutyric acid of the general formula (I) given and defined in Claim 1, whenever prepared by a process claimed in a preceding claim.

15. A pharmaceutical composition according to Claim 8, substantially as hereinbefore described with particular reference to the accompanying Formulation Examples.

F. R. KELLY & CO.,
AGENTS FOR THE APPLICANTS.